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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/835,196	04/13/2001	Barnett S. Pitzele	PHAR 7979/3313US	5348

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EXAMINER

ZUCKER, PAUL A

ART UNIT

PAPER NUMBER

1621

DATE MAILED: 12/30/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/835,196

Applicant(s)

PITZELE ET AL.

Examiner

Paul A. Zucker

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 21 October 2002.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-31 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-31 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                             | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)         | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____                                    |

## **DETAILED ACTION**

### ***Current Status***

1. This action is responsive to Applicants' amendment of 21 October 2002 in Paper No 7.
2. Receipt and entry of Applicants' amendment is acknowledged.
3. Claims 1-31 remain outstanding.
4. The objection to the specification set forth in paragraph 1 of the previous Office Action in Paper No 6 is withdrawn in response to Applicant's amendment.
5. The rejection under 35 USC § 112, second paragraph, set forth in paragraph 2 of the previous Office Action in Paper No 6 is withdrawn in view of Applicants' amendment.
6. The rejection under Obvious-Type Double Patenting set forth in paragraph 5 of the previous Office Action in Paper No 8 is withdrawn in response to Applicants' filing of a terminal disclaimer.
7. The rejection under 35 USC § 103 set forth in paragraph 6 of the previous Office Action in Paper No 8 is withdrawn as moot in view of Applicants' cancellation of all original claims.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

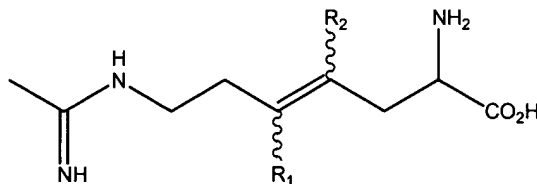
The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

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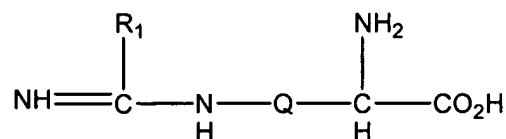
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 1-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beams et al (WO 93/13055-A1 07-1993).

The instantly claimed invention is directed toward the compounds (geometric and stereoisomers) of Formula (I), where  $R_1$  and  $R_2$  may be H or methyl, or their pharmaceutically acceptable salts :



Beams teaches (Page 5, line 26-page 7, line 35) a genus of nitric oxide synthase inhibitors of general formula (I):



Where  $R^1$  may be a  $C_{1-6}$  straight chain or branched alkyl and Q may be an alkylene, alkenylene or alkynylene group having 3-6 carbons. Beams further teaches (Page 5, line 37-page 6, line 1) optional substitution of Q by one or more  $C_{1-3}$  alkyl groups. A preferred embodiment of the compounds is further taught (Page 6 lines 30-36) where  $Q = -(CH_2)_vCH=CH(CH_2)_w-$  where  $v = 0-3$ ;  $w = 0$  to 3; and  $v + w = 2-4$ . The

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instantly claimed compounds correspond to  $v = 2$ ,  $w = 1$  and thus fall within the narrow subgenus suggested by Beams. Beams further teaches (Page 7, lines 1-3) a preferred value for  $R^1$  of methyl. Beams further teaches (Page 3, lines 23-34) that the genus encompasses all stereoisomeric forms (both E,Z and R,S).

Beams teaches (Page 8, line 14 – page 11, line 4) pharmaceutical compositions of the compounds as well. Beams further teaches (Page 16, lines 15 – 25) methods for the selective inhibition of the inducible form of nitric oxide synthase using the compounds of his invention.

Instant claim 28 (1<sup>st</sup> and 2<sup>nd</sup> listed compounds) is obvious over Beams' exemplification (Page 15, lines 1-10, Example 8) of (S)-Z-2-Amino-6-(1-iminoethylamino)-hex-4-enoic acid, hydrochloride. The 1<sup>st</sup> and 2<sup>nd</sup> listed compounds of claim 28 are simply the salts of the adjacent higher homologue with one additional chain methylene unit between the double bond and the amidino group. One of ordinary skill in the art would have the expectation of similar properties for the instant compounds and that of Beams and the instant compounds are therefore obvious over that of Beams.

Thus the instantly claimed compounds, pharmaceutical compositions containing them and the instantly claimed method of use would have been obvious to one of ordinary skill in the art. The motivation for the instantly claimed invention would have been to develop other compounds in the genus taught by Beams and apply them, in

the compositions taught by Beams, to the methods taught by Beams. The expectation for success would have been near certitude since Beams' genus completely embraces the instant compounds which, Beams' teaches, have the instantly desired activity as nitric oxide synthase inhibitors.

***Examiner's Response to Applicants' Arguments with Regard to This Rejection***

9. Applicants' have put forth several arguments with regard to this rejection. The

Examiner responds to these below:

- a. Applicants argue that Beams does not exemplify the compounds of the invention. The Examiner agrees but points out that Beams exemplifies (Page 14, lines 24-31 and page 15, lines 1-10) the adjacent lower homologues over which compounds of the invention are obvious (S)-E-2-Amino-6-(1-iminoethylamino)-hex-4-enoic acid and (S)-Z-2-Amino-6-(1-iminoethylamino)-hex-4-enoic acid.
- b. Applicants argue that Beams teaches a genus with a variable core with numerous variations and that therefore the instant compounds are not obvious over the genus of Beams. The Examiner disagrees with Applicants' conclusion. Beams exemplifies (See above) compounds which are lower adjacent homologues of the instantly claimed compounds. Beams further provides (See rejection, 2<sup>nd</sup> paragraph) clear directions to locate the instantly claimed subgenus of alkyl-substituted compounds within his broader genus of compounds. The identical utility of the compounds of Beams further supports a conclusion of obviousness. Thus the obviousness of the instantly claimed

compounds is supported by more than the fact that the compounds are encompassed by the genus taught by Beams.

- c. Applicants further assert that the Young reference (IDS reference) teaches away from the instant invention. The Examiner disagrees. Young teaches (Paragraph bridging pages 599 and 600) that the effect of structural changes on conformationally flexible molecules is difficult to rationalize and, thus, predict. This constitutes a teaching *toward* the use of conformationally rigid molecules (containing double bonds) in which the effect of structural variation may be more easily rationalized and, therefore, predicted. Notwithstanding the teaching of Young, however, Beams clearly teaches (See paragraph a above) the selection of an olefin function within his variable core.

### ***Conclusion***

10. Claims 1-31 are pending. Claims 1-31 are finally rejected.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing

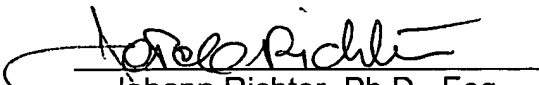
date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul A. Zucker whose telephone number is 703-306-0512. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 703-308-4532. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Paul A. Zucker  
Patent Examiner  
Technology Center 1600  
December 27, 2002

  
Johann Richter, Ph.D., Esq.  
Supervisory Patent Examiner  
Technology Center 1600